REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1 Jan 98	FINAL REPORT 1 May 1992 - 30 Apr 1998

4. TITLE AND SUBTITLE
Microstructural Models of Interactions That Govern Protein Conformations

5. FUNDING NUMBERS
N00014-92-J-1564

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10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The objective of this project was to apply computational methods for microstructures suspended in a viscous liquid, to the calculation of slow dynamics in protein folding and association reactions. A fast Brownian dynamics algorithm was developed, as well as a knowledge-based potential of mean force for interactions protein segments.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Brownian Dynamics, Protein Folding	4
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

FINAL REPORT

GRANT #: N00014-92-J-1564

PRINCIPAL INVESTIGATOR: Dr. Sangtae Kim

INSTITUTION: University of Wisconsin - Madison

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GRANT TITLE: Microstructural Models of Interactions that Govern Protein Conformations: Algorithms for High-Performance Computer Architectures

AWARD PERIOD: 1 May 1992 - 30 April 1998

OBJECTIVE: To apply computational methods for microstructures suspended in a viscous fluid to the calculation of the rates of slower dynamic processes in protein folding and enzyme kinetics.

APPROACH: The configuration space of the process is simplified by
i) treating the surrounding water as a continuum,
ii) modeling the secondary structure elements as rigid bodies, and
iii) computing optimum reaction pathways through configuration space
iv) analyzing the regions around the pathways in order to compute rate constants for the conformation change.

A new hydrodynamic method was developed in our group (CDL-BIEM) to tackle the first two items; a new stochastic method (WEB Dynamics) was developed in our group to handle the last two items.

ACCOMPLISHMENTS: Over the period of this grant, we have completed the development of a computational strategy to simulate the longer time scales in protein dynamics. The two key developments are a fast Brownian Dynamics simulation technique, which we call the Weighted Ensemble Brownian (WEB) Dynamics; and a potential of mean force (thanks to Shankar Subramaniam of NCSA) using knowledge-based bioinformatics applied to the protein databank. A "tool set" for using these potentials, created by A. Rojnuckarin, is accessible via a web browser. The web site is managed by the Computational Biology group at the National Center for Supercomputer Applications (NCSA), www.ncsa.uiuc.edu.

CONCLUSIONS: Given the promising results obtained with knowledge-based potentials (driving folding simulations to correct structure) we have demonstrated the applicability of WEB Dynamics to the longest time scale (slowest) processes in protein folding.

SIGNIFICANCE: The grant period has seen significant developments in our efforts to model (and ultimately predict) protein dynamics that occur on time scales of milliseconds (or slower). The key software tools are available over the world wide web.

PATENT INFORMATION: None

AWARD INFORMATION: The graduate student who worked on this project, Gary Huber, recently accepted a faculty position in the Department of Bioengineering, UC San Diego.

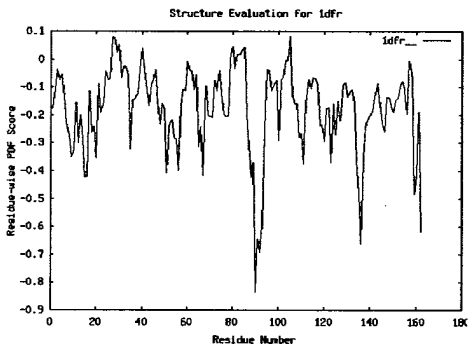
PUBLICATIONS AND ABSTRACTS (for total period of grant):

1. Huber, G. and Kim, S. (1996) Weighted ensemble Brownian dynamics simulations for protein association reactions, Biophys. J. 70:97-110.

2. Mustakis, I., Clear, S., Nealey, P. and Kim, S. (1997) Fluidic self-assembly and self-assembled monolayers. Intl. Symp. on Liquid-Solid Flows, June 22-25, Vancouver.

3. Rojnuckarin, A., Kim, S. and Subramaniam, S. (1998) Brownian dynamics simulations of protein folding: access to millisecond time scales and beyond, Proc. Natl. Acad. Sci. 95:4288-4292.

S. Kim, UW Madison; 1998



http://bioweb.ncsa.uiuc.edu/structure.html

Objectives

Tertiary Protein Dynamics

- Develop computational methods for tertiary level interactions in proteins
- Dynamics: slow, long time scales
- Role of viscous hydrodynamics in folding at tertiary level.

Accomplishments

- Faster Brownian dynamic simulations: Weighted Ensemble Brownian (WEB) Dynamics used in folding (PNAS, **95**, 4288, 1998)
- WWW interface to protein structure evaluation with the knowledge-based potentials (above)

Significance

- Brownian dynamics of protein folding: speed-up by a factor of 100 million
- Applications to biosensors